A positive feedback between p53 and miR-34 miRNAs mediates tumor suppression.

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Public Summary:
miR-34 microRNAs (miRNAs) exhibit frequent alterations in many human tumor types and elicit multiple cell cycle regulatory effects upon overexpression. Unexpectedly, miR-34 deletion alone fails to impair tumor suppressor effects in mice that are regulated through the tumor suppressor protein p53. Here, we demonstrate that miR-34a is part of a positive feedback loop acting on p53, and that miR-34a deficiency strongly promotes tumorigenesis when p53 expression is also reduced. The importance of the p53/miR-34/HDM4 feedback loop is further confirmed by gene expression patterns in human lung adenocarcinomas. Taken together, our results elucidated the intricate cross-talk between p53 and miR-34 miRNAs and revealed an important tumor suppressor effect generated by this positive feedback loop.

Scientific Abstract:
As bona fide p53 transcriptional targets, miR-34 microRNAs (miRNAs) exhibit frequent alterations in many human tumor types and elicit multiple p53 downstream effects upon overexpression. Unexpectedly, miR-34 deletion alone fails to impair multiple p53-mediated tumor suppressor effects in mice, possibly due to the considerable redundancy in the p53 pathway. Here, we demonstrate that miR-34a represses HDM4, a potent negative regulator of p53, creating a positive feedback loop acting on p53. In a Kras-induced mouse lung cancer model, miR-34a deficiency alone does not exhibit a strong oncogenic effect. However, miR-34a deficiency strongly promotes tumorigenesis when p53 is haploinsufficient, suggesting that the defective p53-miR-34 feedback loop can enhance oncogenesis in a specific context. The importance of the p53/miR-34/HDM4 feedback loop is further confirmed by an inverse correlation between miR-34 and full-length HDM4 in human lung adenocarcinomas. In addition, human lung adenocarcinomas generate an elevated level of a short HDM4 isoform through alternative polyadenylation. This short HDM4 isoform lacks miR-34-binding sites in the 3' untranslated region (UTR), thereby evading miR-34 regulation to disable the p53-miR-34 positive feedback. Taken together, our results elucidated the intricate cross-talk between p53 and miR-34 miRNAs and revealed an important tumor suppressor effect generated by this positive feedback loop.